

REMARKS

Applicants respectfully request reconsideration and allowance of all pending claims.

I. Status of the Claims

In this Amendment A, claims 1 and 7 have been amended to more particularly claim certain embodiments of the present disclosure, while claims 19 and 20 have been amended to correct typographical errors. Additionally, claims 21-23 have been added. Accordingly, claims 1-23 are now pending.

Support for the amendments to claims 1 and 7 may be found in the text of the present specification at, for example, paragraph [0042]. Support for the amendments to claims 19 and 20 may be found in these claims as originally filed, as well as in, for example, paragraph [0056] of the present specification. Finally, support for new claims 21-23 may be found in the text of the present specification at, for example, paragraphs [0046] and [0077].

II. 35 U.S.C. 112, second paragraph

Reconsideration is requested of the rejection of claims 19 and 20 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 19 has been rejected because of the phrase "contains less than about 1.0 wt.% during hydrogenation", while claim 20 has been rejected because of the phrase "contains less than about 0.1 wt.% during hydrogenation." The Office has rejected these claims because it is not clear what these phrases are referencing. Applicants have therefore amended claims 19 and 20 to indicate the reaction mixture contains "less than about 1.0 wt.%" or "less than about 0.1 wt.%" *water* (emphasis added). Support for this amendment can be found in the instant Specification at paragraph [0056].

Accordingly, withdrawal of the rejection of claims 19 and 20 is respectfully requested.

III. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1-20 under 35 U.S.C. §103 as being obvious over Rossey et al. (U.S. Patent No. 4,794,185) in view of March, Adv. Org. Chem. 2nd Ed. (1977), p. 402.

A. The Claimed Subject Matter

The present application is generally directed to a novel process for the **direct** synthesis of heteroaryl acetamides. More particularly, the independent claims of the present application are directed to a process for preparing heteroaryl acetamides that are biologically active by **directly hydrogenating** heteroaryl α -hydroxyacetamides in a **reaction mixture** that includes a strong acid, a halide, and a precious metal catalyst. (See, e.g., paragraph [0007] of the present specification.) Desirably, in order to minimize undesirable side reactions, the amount of water in the reaction mixture at the initiation of, and during, hydrogenation is also minimized (see paragraph [0054]).

Accordingly, it is to be noted that independent claims 1, 7 and 13 are directed, in relevant part, to a process for the preparation of a heteroaryl acetamide from a heteroaryl α -hydroxyacetamide that comprises:

directly hydrogenating a heteroaryl α -hydroxyacetamide in the presence of hydrogen gas in a **reaction mixture** comprising a solvent system, the **heteroaryl α -hydroxyacetamide**, at least one strong acid, a halide, and a **precious metal catalyst**, wherein the reaction mixture has a molar ratio of the starting heteroaryl α -hydroxyacetamide to water at the initiation of hydrogenolysis or at least about 2:1 . . . (Claim 1, emphasis added);

forming a **reaction mixture** by combining a **heteroaryl α -hydroxyacetamide**, a strong acid, a halide, a **precious metal catalyst** and a water scavenger and contacting the

reaction mixture with a hydrogen source . . . (Claim 7, emphasis added); and,

directly hydrogenating a heteroaryl α -hydroxyacetamide in the presence of hydrogen gas in a **reaction mixture** comprising a solvent system, the **heteroaryl α -hydroxyacetamide**, at least one strong acid, a halide and a **palladium on carbon catalyst**, wherein the reaction mixture contains less than about 2.5 wt.% water . . . (Claim 13, emphasis added).

New claims 21-23, which depend from claims 1, 7 and 13, respectively, call for a reaction mixture that has a halide concentration of less than about 2.1×10^{-5} M. As noted in the text of the specification, Applicants' experience has shown that a halide concentration in excess of this concentration is not preferred because it negatively impacts the yield of the reaction (see, e.g., paragraph [0046] and [0077]).

B. The Cited Art

Rossey et al. disclose a **two step process** for the preparation of an imidazopyridine acetamide. The process includes first reacting an imidazopyridine with a dialkoxyalkylamide to produce an imidazopyridine α -hydroxyacetamide intermediate. The intermediate is then converted to an α -chloroacetamide hydrochloride, and subsequently reduced to produce the desired imidazopyridine acetamide. Specifically, the imidazopyridine acetamide is prepared by first reacting an imidazopyridine (formula (II)) with a compound of formula (III) at a temperature of 20° to 100°C in the presence of an acid and in a solvent to obtain a compound of formula (IV) and then reacting the compound of formula (IV) with a compound releasing chlorine, such as thionyl chloride, phosphoryl chloride, phosgene or oxalyl chloride, in a solvent to obtain the α -chloroacetamide hydrochloride (see, e.g., column 7, structure (V)). This chlorinated compound (e.g., structure (V)) is then reduced using a **reducing agent** such as NaBH₄, Zn(BH₄)₂, KBH₄, LiBH₄, a dithionite or a derivative of any of these.

March discloses hydrogenolysis of alcohols by catalytic hydrogenation. Specifically, alcohols, such as **benzyl-type alcohols**, are said to undergo a hydrogenation reaction using catalysts such as copper chromite and palladium-on-charcoal.

The Office asserts that the claimed process is obvious in view of the combination of Rossey et al. and March because Rossey et al. teach a process similar to the one claimed, the Rossey et al. process comprising a reaction mixture including NaBH_4 as a catalyst, SOCl_2 , 1,2-dichloromethane, water and sodium carbonate. Furthermore, the Office asserts that while Rossey et al. teach a two step process, March teaches hydrogenolysis of alcohols using a one step process using a hydrogen source and palladium on carbon as the catalyst. As such, Applicants' process is merely a selective combination of teachings of the prior art processes done in a manner obvious to one of ordinary skill in the art; that is, Applicants' have done no more than combine separate but well-known inventions. Applicants respectfully disagree.

As specifically noted by the Office, Rossey et al. fail to teach a **single step, direct** hydrogenation process for heteroaryl acetamide. Specifically, as noted above, Rossey et al. disclose a process wherein they must first convert an imidazopyridine α -hydroxyacetamide intermediate to α -chloroacetamide; then, in a **second** separate step, they reduce the α -chloroacetamide to an imidazopyridine acetamide using sodium borohydride.

Furthermore, it is to be noted that Rossey et al. also **fail to disclose or suggest** a reaction mixture that includes a heteroaryl α -hydroxyacetamide and a catalyst. Specifically, although Rossey et al. disclose separately using some of the components of the claimed reaction mixture in individual reaction steps, nowhere do they disclose or suggest using **one reaction mixture** that includes α -chloroacetamide and a catalyst. Rather, Rossey et al. disclose a reaction mixture that includes α -chloroacetamide in methanol, and sodium borohydride in water. Sodium borohydride is not a precious metal catalyst; in fact, it is not a catalyst at all. Rather, it is a reducing agent that actively participates in the reaction.

It is to be still further noted that, with respect to claims 1 and 13, Rossey et al. disclose, in Example 3, a reaction mixture that includes a concentration of water **significantly higher** than the water concentration in the reaction mixtures of claim 1 and 13. More specifically, Rossey et al. disclose a reaction mixture wherein: (i) contrary to claim 1, the molar ratio of water significantly **exceeds** that of, in this case, the α -

chloroacetamide (the ration being in excess of 60:1), and (ii) contrary to claim 13, the concentration of water in the reaction mixture **significantly exceeds** 2.5 wt.% (the concentration being in excess of 30 wt.%).

March fails to overcome the above shortcomings of Rossey et al. Specifically, while March is directed to a single step hydrogenation process of alcohols, such as benzyl-type alcohols, March clearly **fails to disclose or suggest** the hydrogenation of **heteroaryl α -hydroxyacetamide**, in order to prepare **heteroaryl acetamides**.

Furthermore, with respect to new claims 21-23, which depend from claims 1, 7 and 13, respectively, it is to be noted that these claims call for a reaction mixture that has a halide concentration of less than about 2.1×10^{-5} M. Applicants' experience has shown that a halide concentration in excess of this concentration is not preferred because it negatively impacts the yield of the reaction. Notably, Rossey et al. prepares a reaction mixture that includes α -chloroacetamide hydrochloride (structure (V)); the reaction mixture thus has a halide concentration that significantly **exceeds** 2.1×10^{-5} M. In addition, March provides **no details** at all regarding component concentrations in the disclosed reaction mixture.

C. The Claimed Subject Matter is Not Obvious

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2142 requires a clear articulation of the reasons why the claimed invention would have been obvious. Specifically, to reject a claim based on this rationale, the Office must articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness because each and every element of the claims has not been disclosed or suggested by

the cited references, and/or because there is no motivation to modify/combine the references in order to achieve the claimed subject matter.

Applicants submit that nowhere in the cited combination of references is a process disclosed or suggested for directly hydrogenating a heteroaryl α -hydroxyacetamide in a reaction mixture including, among other things, a heteroaryl α -hydroxyacetamide. As noted above, March discloses, at most, direction hydrogenation of benzyl-type alcohols. Rossey et al. disclose a process wherein they must first convert an imidazopyridine α -hydroxyacetamide intermediate to α -chloroacetamide; then, in a **second** separate step, they reduce the α -chloroacetamide to an imidazopyridine acetamide using sodium borohydride. Accordingly, March is completely silent with respect to the claimed process, while Rossey et al. arguably **teach away** from the claimed process, given that a two step process is used that involves the hydrogenation of an α -chloroacetamide rather than an α -hydroxyacetamide.

Applicants additionally submit that, with respect to claims 1 and 13, the cited combination of references additionally fail to disclose or suggest the water concentration aspect of the recited reaction mixture. More specifically, as previously noted, March is completely silent with respect to the component concentrations, and/or the presence water, in the disclosed reaction mixture, while Rossey et al. arguably **teach away** from the claimed process, given that the disclosed reaction mixture contains significantly more water than is allowed for in these claims.

Furthermore, Applicants respectfully submit there is no motivation to combine the cited references. Specifically, March is directed to a different chemical reaction as compared to Rossey et al. (as well as Applicant's claimed processes); that is, March is directed to hydrogenating **aromatic alcohols**, which is separate and distinct from the hydrogenating α -chloro-substituted heteroaromatic compounds, such as is taught by Rossey et al. Applicant therefore submits there is simply **no motivation** for one of ordinary skill in the art to select the specific features necessary to arrive at the claimed processes from the separate processes disclosed in the cited references.

In fact, Applicant respectfully submits the present rejection is the result of **impermissible hindsight analysis**, because the Office appears to have used the

invention as defined by the claims as a guide to pick and choose from among the steps provided in the processes taught in Rossey et al. and in March in order to reject the present claims. In this regard it is to be noted that the Court has stated:

There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge can not come from the applicant's invention itself.

(See *In re Oetiker*, 977 F.2d at 1447; 24 U.S.P.Q.2d at 1446).

The Court has also stated that "[w]hen a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references." (See *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998).) Many inventions are combinations of old elements. (*Id.* at 1457.) If identification of each element of a claim in the prior art were all that were necessary to negate patentability, the Office could simply "use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. (*Id.*) The decision in *Rouffet* is instructive in this regard. Although the Court concluded that the cited combination of references disclosed all the elements of Rouffet's claims, the Court nevertheless reversed the Board's affirmation of the Office's rejection, holding that "the Board reversibly erred in determining that one of skill in the art would have been motivated to combine these references in a manner that rendered the claimed invention obvious." (*Id.* at 1457.)

In view of the foregoing, Applicant respectfully submits independent claims 1, 7 and 13 are in fact patentable over the cited combination of references, and therefore that the present rejection is improper. Applicants additionally submit dependent claims 2-6, 8-12, and 14-23 are patentable over the cited references for at least the reasons set forth above with respect to the claims from which they depend, and/or the additional limitations present therein. In particular, Applicants respectfully submit that claims 21-23 are patentable over the cited combination of references because (i) Rossey et al. arguable **teaches away** from recited reaction mixture, inasmuch as the reaction mixture they disclose has a halide concentration that significantly **exceeds** 2.1×10^{-5} M, and (ii)

March provides **no details** at all regarding component concentrations in the reaction mixture.

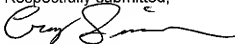
Reconsideration and allowance of all pending claims is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Amendment A in Response to Non-final Office Action, including the fees associated with the submission of three additional dependent claims.

Respectfully submitted,



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